Current Topics in Virology

Original Article

Antiretroviral pre-exposure prophylaxis (PrEP) for avoiding HIV in high-risk individuals

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ABSTRACT

This study revised the search strategy and conducted an updated search of MEDLINE, the Cochrane Central Register of Controlled Trials and EMBASE in April 2017. The study also searched the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov for ongoing trials. Data concerning outcomes, details of the interventions, and other study characteristics were extracted by two independent authors using a standardized data extraction form. Relative risk with a 95% confidence interval (CI) was used as the measure of effect. 12 randomized controlled trials that meet the criteria for the review were identified. Six were ongoing trials, four had been completed and two had been terminated early. Six studies with a total of 9849 participants provided data for this review. The trials evaluated the following: daily oral tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) versus placebo; TDF versus placebo and daily TDF- FTC versus intermittent TDF-FTC. One of the trials had three study arms: TDF, TDF-FTC and placebo arm. The studies were carried out amongst different risk groups, including HIV-uninfected men who have sex with men, serodiscordant couples and other high-risk men and women.

KEYWORDS: PrEP, high-risk groups, systematic research, literature research, DataFax, PICO.

Introduction

Antiretroviral therapy (ARV) that achieves virologic suppression renders the risk of sexual transmission to HIV-uninfected partners insignificant, lending hope that "treatment as prevention" (TasP) can arrest the epidemic. Moreover, persons who appropriately use tenofovir-emtricitabine (TDF-FTC) for pre-exposure prophylaxis (PrEP) can avoid HIV acquisition, and its use is increasing in resource-rich countries. Pre-exposure prophylaxis (PrEP) is a daily course of antiretroviral drugs (ARVs) that can protect HIV-negative people from HIV before potential exposure to the virus.

Trials have shown that, when taken consistently and correctly, PrEP is very effective and reduces the chances of HIV infection to near-zero. This has led some to describe PrEP as a 'game changer' for HIV prevention.

The implications of rising sexually transmitted infection (STI) rates require reassessment of the alignment and prioritization of HIV research funding, public health policy, and community engagement and give rise to numerous questions. Are STIs an inevitable byproduct of biomedical HIV control, and should the answer change our view of sexual health? Do we need to think differently about management of non-HIV STIs (screening, diagnosis, treatment, partner management) in populations at risk for HIV? Is high STI incidence likely to undermine success of TasP or PrEP in the long term or in certain populations? Should new approaches focus on broader spectrum prevention (agents that inhibit HIV and other viruses)? What are the broad implications, including funding and trial design, for clinical STI research?

While PrEP can provide very effective protection against HIV, it does not provide protection against

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other sexually transmitted infections (STIs) and blood-borne illnesses such as Hepatitis C, syphilis, and gonorrhoea. The effectiveness of PrEP is closely linked to adherence - if someone taking PrEP regularly misses daily doses, their risk of HIV infection will increase substantially. It is therefore important that any programme offering PrEP provides it as part of a combination package of prevention initiatives, based on an individual's circumstances - with support and advice on the importance of PrEP adherence [1].

In 2015, recognising that PrEP has potential population-wide benefits, the World Health Organization (WHO) released new guidelines and a policy brief recommending that PrEP should be offered as a choice to people who are at substantial risk of HIV infection as part of a combination HIV prevention programme. Previously, PrEP was only recommended for certain key affected populations such as sex workers, men who have sex with men (sometimes referred to as MSM) and people who inject drugs (sometimes referred to as PWID). UNAIDS broadly defines priority populations for PrEP as groups with an HIV incidence of about 3 per 100 person-years or higher [2, 3].

The United Nations General Assembly's 2016 Political Declaration on HIV and AIDS includes a commitment to providing three million people at higher risk of HIV infection with PrEP by 2020. However, as of October 2016, just 100,000 people were enrolled on it. Most people on PrEP live in the USA, although a significant number of people across the world are also thought to be accessing it through the internet.

Although the number and scope of PrEP activities is increasing globally, the scale and coverage of PrEP outside the USA currently remains extremely limited.

Truvada, a single pill that is a combination of ARVs tenofovir and emtricitabine, is currently the only drug approved for use as PrEP.

Key points

- Pre-exposure prophylaxis (PrEP) is a daily course of antiretroviral drugs (ARVs) taken by HIV- negative people to protect themselves from infection.
- Evidence shows that, when taken consistently and correctly, PrEP reduces the chances of HIV infection to near-zero.
- PrEP is cost effective, and there is growing demand for it from people at higher risk of HIV infection, but the scale and coverage outside the USA currently remains extremely limited.
- PrEP does not protect against other STIs and hence it needs to be delivered as part of a comprehensive package of HIV/STI prevention services.
- PrEP's effectiveness decreases rapidly if not taken regularly as prescribed, and hence addressing the barriers preventing adherence is key to success.

What are the data?

Incident chlamydia, gonorrhea, and syphilis have risen sharply among men in the United States and other industrialized countries, with syphilis disproportionately high among MSM. Reports of gonorrhea at the rectal and pharyngeal sites are increasing disproportionately compared to urethral sites, partially due to enhanced screening of extragenital sites [4]. This may be coincident with increased frequency of unprotected anal sex: in San Francisco, increasing proportions of condomless anal sex amomg MSM were reported in the National Health Behavior Study from 2005-2014, and persons attending sexually transmitted disease clinics during the years 2007-2013 reported increases in the number of recent male sex partners [4]. Motivation for decreased condom use may include confidence that use of ARV for prevention attenuates transmission risk or the belief that HIV is no longer a serious health concern.

In studies of TDF-FTC PrEP involving MSM, high rates of incident STI have been observed [5, 6]. Increasing rates of condomless sex in the context of PrEP may be only part of the explanation for this. STI increases among MSM antedated the PrEP era, including increasing rates among already HIV-infected MSM [7]. Recognition of the impact of treatment on transmission increased over roughly the same time period as PrEP uptake increased and likely also impacted sexual behavior among MSM. By definition, PrEP users are generally individuals with substantial risk for STIs, as well as HIV. Moreover, routine STI testing has been part of these PrEP studies, providing opportunity for enhanced detection of asymptomatic infections.

Are these trends, if widely representative, necessarily bad for STI control? Some modeling suggests that more frequent screening among MSM using PrEP might over time drive down rates of STI, assuming screening increases substantially and STIs are appropriately treated; there is also the possibility that more treatment of gonorrhea might actually promote faster spread of antibiotic resistance. Admittedly, evidence from randomized controlled trials would be needed to study these scenarios [4].

Pre-exposure prophylaxis (PrEP) in HIV-uninfected individuals with high-risk behavior

The global incidence of human immunodeficiency virus (HIV) infection has decreased by 15% over the past years but is still too high. Despite current programs to reduce the incidence of HIV infection, further approaches are needed to limit this epidemic. Oral antiretroviral pre-exposure prophylaxis (PrEP) is currently one of the most discussed possible prevention methods. This literature study demonstrates whether oral antiretroviral chemoprophylaxis in HIV-uninfected individuals with high-risk behavior reduces the transmission of HIV. The subjects of the study were HIV-uninfected individuals with high-risk behavior. Intervention was oral PrEP with tenofovir disoproxil fumarate (TDF) alone or plus emtricitabine (FTC) versus placebo. The primary outcome was the HIV incidence among this high-risk group. Secondary outcomes were adherence to PrEP, frequency and type of adverse effects. Ten studies were identified from which five randomized control trials (RCTs) were included after screening. The results from three out of five trials showed a reduction, but two trials showed no protection in acquiring HIV infection. There were no significant differences in adverse events. The adherence was different among different groups and affected the outcome of the studies. In conclusion, this prophylaxis might offer protection when used in combination with intense monitoring and guidance in uninfected individuals with a high risk of HIV acquisition. However, there are still many unresolved questions. Drug adherence seems to be a crucial factor in the effectiveness of PrEP. Therefore, individual risk behavior remains an important determinant for success in the prevention of HIV transmission.

Study 1: Objective of study

Systematic review to evaluate the effects of oral antiretroviral pre-exposure prophylaxis (PrEP) in preventing HIV infection in HIV-uninfected persons at high risk of becoming infected.

Studies

Randomized controlled trials (RCT).

Population

Populations at high risk of HIV infection, e.g. commercial sex workers, individuals in serodiscordant relationships, injection drug users, men who have sex with men (MSM), sexually active young adults.

Intervention

Oral antiretroviral regimens including tenofovir (TDF) vs. placebo or no treatment; TDF with emtricitabine (FTC) vs. placebo or no treatment; TDF only versus TDF + FTC; or any other oral PrEP regimen.

Main outcome measures

HIV incidence, adherence to PrEP, sexual risk behavior and adverse events.

Search strategy

Standard Cochrane HIV/AIDS Group search strategies were used, along with a range of relevant keywords and medical subject heading (MeSH) terms. There were no limits to language or publication status.

Databases searched included the Cochrane Central Register of Controlled Trials, EMBASE, and PubMed, as well as online archives of major HIV/AIDS conference abstracts. The date range for the searches of the peer-reviewed literature was from January 1980 to April 2017. Archived conference abstracts were searched from 1985 to 2012. The World Health Organization (WHO)'s International Clinical Trials Registry Platform (ICTRP) and the National Institutes of Health's ClinicalTrials.gov were also searched for ongoing trials. The reviewers checked reference lists of included trials.

The Patient/Population, Intervention, Comparison, Outcome (PICO) method was used in this study,

which allows you to take a more evidence-based approach when searching bibliographic databases and conducted a comprehensive search to identify all relevant studies. Patients (P) were HIV-uninfected individuals with high-risk behavior, namely in serodiscordant relationships, commercial sex workers, intravenous drug users and MSM. Pregnant women were excluded. The intervention (I) was an oral PrEP regime with TDF-FTC. The studies involving topical application of antiretroviral agents such as vaginal gels were excluded. For the comparison (C) an oral PrEP regime was compared with placebo or no treatment. The primary outcome (O) was HIV incidence among this high-risk group. Secondary outcomes were adherence to PrEP, safety and frequency and type of adverse effects or complications. The titles and abstracts of the search output from the different databases were screened to identify eligibility of the studies. Full-text articles were obtained for all citations identified as potentially eligible. Extracted information included the study design, population, intervention details, namely type of drug, comparator, dose, duration and route of administration, and primary and secondary outcomes.

Searches, screening and data extraction

One trial was included from the previous version of this study. A total of 2,684 new records were retrieved. Standard Cochrane methods were used in the screening process and in data collection. Two reviewers working independently identified 12 relevant studies, six of which were ongoing. Eight trials met the review's inclusion criteria. Two of these trials had not yet been published in the peer reviewed literature but the reviewers contacted investigators for necessary data. Two reviewers working independently extracted data from included trials.

Statistical analysis

Data were collected on case-report forms and faxed to a DataFax server at DF/Net Research. It was determined that the observation of 85 incident HIV infections would yield a power of at least 80% with a one-sided alpha level of 0.05 to reject a null hypothesis of efficacy of 30% or less if the true efficacy were 60% or more. The modified intention-to-treat analysis included available data for all subjects except those with HIV RNA detected in their enrollment sample. The as-treated analysis used a time-dependent covariate indication as to whether the subject was known to fall below the prespecified level of study-drug compliance (50%) on any of the following: records of study-drug dispensation alone, pill-use calculation based on study-drug dispensation and returns, and subjects' self-report. For the as-treated analysis, pills from unreturned bottles were assumed to have been taken, and late visits were included in the analysis if the last dispensation allowed pill use on 50% or more of days. Safety analyses included all subjects.

Results

The eight included trials involved HIV-uninfected participants from several key populations: MSM aged ≥18 years (n = 2,499), high-risk women aged 18-35 years (n = 936), high-risk men and women (n = 144), 4758 serodiscordant heterosexual couples (n = 9,516 individuals), heterosexual men and women aged 18-39 (n = 1200) and high-risk women aged 18-35 years (n = 2,120). Trials were conducted in Botswana, Brazil, Cameroon, Ecuador, Ghana, Kenya, Nigeria, Peru, South Africa, Tanzania, Thailand, United States and Zimbabwe [5-10].

Five trials were included. Frequency of HIV infection: In USA, after 3 rounds of treatment of all community members for STIs, the rate ratio of incident HIV infection was 0.97 (95%CI 0.81 to 1.16), indicating no effect of the intervention. In South Africa, the incidence of HIV infection in the intervention groups (strengthened syndromic management of STIs in primary care clinics) was 1.2% compared with 1.9% in the control groups (OR = 0.58, 95% CI 0.42-0.70), corresponding to a 38% reduction (95%CI 15% to 55%) in HIV incidence in the intervention group. In the newest trial by Kamali *et al*., the rate ratio of behavioral intervention & STI management compared to control on HIV incidence was 1.00 (0.63-1.58, p = .98). These are consistent with Rakai data showing no effect of intervention. Frequency of STIs: In both USA and South Africa, there was no significant reduction in gonorrhoea, chlamydia, urethritis, or reported STI symptoms among intervention communities. The prevalence ratio of syphilis between intervention and control groups in Rakai was 0.8 (95%CI 0.71-0.89), of trichomoniasis was

0.59 (0.38-0.91), and of bacterial vaginosis was 0.87 (0.74-1.02) In Mwanza, the prevalence of serologically diagnosed syphilis in the intervention community was 5% compared with 7% in the control community at the end of the trial (adjusted relative risk - 0.71 (95%CI 0.54-0.93)). Rate ratio for gonorrhea was 0.29 (0.12-0.71, p = 0.016), active syphilis was 0.53 (0.33-0.84, p = 0.016). There was a trend towards significance with intervention on the use of condoms with the last casual partner; the rate ratio was 1.27 (1.02-1.56, p = 0.036). Quality of treatment: In Cameroon, following training of pharmacy assistants in STI syndromic management, symptoms were recognized as being due to an STI in 65% of standardized simulated patients (SSPs) visiting intervention and 60% of SSPs visiting control pharmacies (p = 0.35). Medication was offered without referral to a doctor in most cases (83% intervention and 78% control, p = 0.61). Of those SSPs offered medication, only 1.4% that visited intervention pharmacies and only 0.7% that visited control pharmacies (p = 0.57) were offered a recommended regimen. However, education and counseling were more likely to be given to SSPs visiting intervention pharmacies (40% vs 27%, p = 0.01). No SSPs were given partner cards or condoms. In USA, following the intervention targeting primary care clinic nurses (strengthened STI syndromic management and provision of STI syndrome packets containing recommended drugs, condom, partner cards and patient information leaflets), SSPs were more likely to be given recommended drugs in intervention clinics (83% vs 12%, p < 0.005) and more likely to be correctly case managed [given correct drugs, partner cards and condoms] (88% vs 50%, p < 0.005). There were no significant differences in the proportions adequately counseled (68% vs 46%, p = 0.06), experiencing good staff attitude (84% vs 58%, p = 0.07), and being consulted in privacy (92% vs 86%, p=0.4). There was no strong evidence of any impact on treatment-seeking behavior, utilization of services, or sexual behavior in any of the four trials.

Primary outcomes

HIV incidence: Four trials that compared TDF-FTC vs. placebo reported HIV incidence. All but one, "FEM- PrEP" [11] showed a reduced HIV incidence, and the reviewers suggest that subjects in this trial's intervention arm were insufficiently adherent to TDF-FTC. In addition, the reviewers noted that this trial had been stopped early for futility (relative risk [RR] 0.95, 95% CI 0.60 to 1.52).

In meta-analysis of the four trials, HIV incidence was significantly lower in subjects who received TDF-FTC (RR 0.51, 95% CI 0.30 to 0.86). There was substantial statistical heterogeneity (I2 = 73%, p = 0.01). One of the four trials was in an MSM population [12]; HIV incidence in this trial was reduced by 44% (RR 0.56, 95% CI 0.38 to 0.84). In meta-analysis of the three trials in heterosexual populations, HIV incidence was reduced by 53% (RR 0.47, 95% CI 0.21 to 1.08).

Two trials that compared TDF only vs. placebo reported HIV incidence [13]. In meta-analysis of the two trials, HIV incidence was significantly lower in subjects who received TDF (RR 0.38, 95% 0.23 to 0.63). There was no significant statistical heterogeneity (I2 = 0%, p = 0.88).

In gender pre-specified subgroup meta-analysis, TDF-FTC significantly reduced new HIV infections in both men and women. However, TDF-FTC was marginally more efficacious in men (RR 0.18, 95% CI 0.08 to 0.43) than in women (RR 0.43, 95% CI 0.24 to 0.77) (p-value for interaction = 0.11).

A comparison of TDF-FTC vs. TDF only showed no significant difference in HIV incidence (RR 0.72, 95% CI 0.36 to 1.47).

Adherence: Reported adherence in the FEM-PrEP trial's intervention arm was 95%. Based on pill count, however, adherence was 86% in the intervention arm; measurement of TDF-FTC in blood levels suggested that adherence was significantly lower. Only 7/33 (21%) of HIV-infected subjects and 377/991 (38%) of uninfected subjects had detectable TDF-FTC in their blood. There was a similar disparity between reported adherence and objective measurements in the trial among MSM [14-16] with a median range of 89-95% adherence after eight weeks, but TDF-FTC was detectable in the blood of only 22/43 (51%) of HIV-uninfected subjects. Adherence by pill count in one trial [17] was 97%. Self-reported adherence in two trials ranged from 83.7%-84.1%. One trial did not report on adherence [18].

Sexual behavior: Two trials [19, 20] reported similar sexual practices across study arms, and one

of these trials [21] reported no significant differences in the number of subjects with non-HIV sexually transmitted infections. Another trial described self-reported decreases in the number of coital acts per week and in the number of sexual partners in the past month, and self-reported increases in condom use.

Adverse events: All the TDF-FTC trials reported significantly higher rates of nausea and vomiting in the TDF-FTC arm vs. placebo. One trial reported the development of renal insufficiency in 26 subjects (2%) in its TDF-FTC arm vs. 15 (1%) in the placebo arm ($p = 0.08$), which was reversible on discontinuation of the drug. Mild-to-moderate increases in alanine amino transferase (ALT) were noted in some subjects in another trial [22]. None of the other increases in study-related adverse events in any of the trials was statistically significant.

Does pre-exposure prophylaxis for HIV prevention in men who have sex with men change risk behavior?

A systematic review of the state of the evidence regarding the association of pre-exposure prophylaxis with condom use, sexually transmitted infection incidence and change in sexual risk behaviors in men who have sex with men was conducted. A structured search of databases resulted in 142 potential citations, but only 10 publications met inclusion criteria and underwent data abstraction and critical appraisal. An adapted Cochrane Collaboration domain-based assessment tool was used to critically appraise the methodological components of each quantitative study, and the Mixed Methods Appraisal Tool was used to critically appraise qualitative and mixed-methods studies.

Condom use in men who have sex with men using pre-exposure prophylaxis is influenced by multiple factors. Studies indicate rates of sexually transmitted infections in treatment and placebo groups were high. Pre-exposure prophylaxis did not significantly change sexually transmitted infection rates between baseline and follow-up. Reporting of sexual risk improved when questionnaires were completed in private by clients. Data showed that pre-exposure prophylaxis may provide an opportunity for men who have sex with men to access sexual health care, testing, treatment and counselling services.

The perception among healthcare providers that pre-exposure prophylaxis leads to increased sexual risk behaviors has yet to be confirmed. In order to provide effective sexual health services, clinicians need to be knowledgeable about pre-exposure prophylaxis as an HIV prevention tool.

Conclusions

In the era of biomedical HIV prevention, STIs are increasing in many populations, offering new challenges and opportunities. PrEP has introduced a tension between HIV and STI prevention that needs to be articulated and confronted: condomless sex is becoming more frequent, and anxiety about HIV acquisition risk can be considerably lessened. That STI incidence is increasing concurrent with the positive, affirming aspects of PrEP and TasP is a reality that should be recognized as an opportunity to promote sexual health, embrace diversity of sexual expression, and develop creative, efficient, comprehensive approaches to the study of STIs for the next decade. This will entail reexamination of the research priorities that span funding organizations, as well as allocation of funding in its current form. Studies primarily aimed at biomedical HIV prevention should incorporate efficient designs to include STI as well as HIV. Finally, it will be critical to engage communities in an active dialogue to advance mutual understanding of how these disease trends are perceived, studied, and managed.

The author concludes that the use of oral TDF alone or a TDF-FTC combination as pre-exposure prophylaxis reduces the risk of acquiring HIV in high-risk individuals.

Quality of the evidence

The author used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [23] to assess evidence quality. GRADE ranks the quality of evidence on four levels: “high”, “moderate”, “low” and “very low”. Evidence from randomized controlled trials starts at “high”, but can be downgraded based on study limitations, inconsistency of results, indirectness of evidence, imprecision or for reporting bias. Evidence from observational studies starts at “low”, but can be upgraded if the magnitude of treatment effect is very large, if there is a significant

dose-response relation, or if all possible confounders would decrease the magnitude of an apparent treatment effect. Evidence from observational studies can also be downgraded. The reviewers found the quality of evidence to be moderate for the outcomes of HIV incidence and adverse events. The quality of evidence was graded down for imprecision, due to the small number of events in treatment arms.

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CONFLICT OF INTEREST STATEMENT

This paper does not contain any conflict of interest.

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